REMARKS/ARGUMENTS

New claim 46 is supported at e.g., p. 13, lines 4-7. New claim 47 is directed to method of producing the mutant antibody of claim 30. The method steps are supported by e.g., original claim 1, and the specification at p. 24, lines 29-37. Claims 48 and 49 add elements to claim 47 in parallel with claims 32 and 46 respectively.

Rejection of claims 30-45 under 35 USC 112, first paragraph

The Examiner attempts to distinguish *Wands* by alleging that it is routine to screen hybridomas for antibodies because one has an expectation of obtaining an antibody, whereas it is not routine to remove a glycosylation site and obtain an antibody with increase affinity. The Examiner alleges that it is not routine to screen antibodies to obtain an outcome that is quite rare. The Examiner alleges that one could not predict without undue experimentation whether removal of any glycosylation site in any antibody would result in an increased affinity. The Examiner cites WO 03/16466, which he erroneously refers to as "prior art," as teaching that it is unpredictable whether glycosylation would affect affinity positively, negatively or not all. The Examiner also alleges that the specification does not teach mutations within the entire variable region, and provides no direction or guidance how to produce antibodies as claimed. This rejection is respectfully traversed.

The Examiner has asserted that the specification provides no direction or guidance regarding how to produce antibodies as broadly defined by the claims, particularly throughout the variable regions. However, other than his comments regarding the unpredictability of individual substitutions (which will be addressed below), the Examiner has not commented on the extensive guidance that is provided by the specification as was discussed in detail in the last response. This guidance includes a specific strategy for making mutations in CDR regions depending on whether the epitope bound by the antibody includes carbohydrate. Briefly to recap, the guidance includes the following.

The specification teaches that "when the parent immunoglobulin sequence contains a glycosylation site in a V region framework, particularly in a location near the antigen

binding site (for example, near a CDR), the glycosylation site sequence is mutated (e.g., by site-directed mutagenesis) to abolish the glycosylation site sequence, typically by producing a conservative amino acid substitution of one or more of the amino acid residues comprising the glycosylation site sequence (page 12, line 30 to page 13, line 7). The glycosylation sites can be readily identified (see page 6, line 36 to page 7, line 30 of the specification). The specification teaches that when the parent immunoglobulin sequence contains a glycosylation site in a CDR, and the parent immunoglobulin specifically binds an epitope that contains carbohydrate, that glycosylation site is preferably retained. If the parent immunoglobulin specifically binds an epitope that comprises only polypeptide, glycosylation sites occurring in a CDR are preferably eliminated by mutation (e.g., site-directed mutation)." (New claims 46 and 48 are specifically drawn to mutation of immunoglobulins of this type.) Once a putative glycosylation site is identified, the specification teaches to follows routine molecular biology techniques to make a mutant construct to eliminate such glycosylation site, produce the mutant antibody and measure its affinity (see specification at p. 16, lines 8-17).

The Examiner does not allege that any of the steps required to produce mutant antibodies or determine their binding affinity would not be routine for the artisan. Rather, the Examiner finds fault only in that this teaching does allow one to determine whether every substitution of every glycosylation site in every antibody increases affinity without performing screening. As will be shown, such a requirement is contrary to the *Wands* decision.

The Examiner's alleged distinction over *Wands* does not exist. The screening performed in *Wands* was not simply to identify hybridomas producing antibodies, but to identify antibodies having an affinity in excess of 10^9 M^{-1}. One would expect a broad range of binding affinities in a total pool of hybridomas. Moreover, it was unpredictable which hybridomas produced antibodies with affinities greater than 10^9 M^{-1} until the screening had been performed. Nevertheless, the court found that "practitioners of this art are prepared *to screen negative hybridomas in order to find one that makes the desired antibody*" (858 F.2d at 740, emphasis supplied). The *Wands* patent was held to be enabled establishing the principle that the enablement requirement can be fulfilled by the possibility of identifying a subset of antibodies having a desired property from a larger class by routine screening.

The present facts and circumstances are similar to *Wands*. In both cases, antibodies to be screened are generated by well-known and routine technology (in *Wands* hybridoma technology, and here standard mutagenesis procedures). In both cases antibodies are screened for a desired affinity. There is no evidence that the number of antibodies that would have to be screened to obtain one with the desired affinity is any greater in the present methods than in *Wands*. In the screening performed in *Wands,* as in any other screening procedure, one does not know which members of a larger class have the desired property until the screening has been performed. The remarks at p.3 of WO 03/016466 regarding the unpredictability of binding affinity until it has been determined merely illustrate this broad truism for an antibody produced in accordance with the methods disclosed in the present application. Such was not detrimental to enablement in *Wands*, because those in the art are prepared to perform routine screening of large number of antibodies. It is respectfully submitted that the same is true of the present claims.

The asserted requirement that applicants identify in advance which substitutions in which antibodies increase binding affinity is submitted to be particularly inappropriate for the new method claims (47-49). These claims include a step of determining that the affinity of the antibody is increased. Such a step would be redundant if one must already know this information before the method is performed.

For all of these reasons, withdrawal of the rejection is respectfully requested.

Claims 30-45 stand rejected under 35 USC 112, first paragraph as allegedly failing to comply with the written description requirement. The Examiner alleges the specification only teaches one example of removal of a glycosylation site that results in increased affinity. The Examiner cites *Vas-Cath* as teaching that the standard for written description is possession of what is now claimed. The Examiner also cites *Fiers v. Revel*, *Amgen v. Chugai* and *Fiddes vs. Baird* for the proposed that one cannot describe what cannot be conceived. This rejection is respectfully traversed.

The facts and circumstances underlying the present claims are considerably different than those in the cases cited by the Examiner. As noted by MPEP 2163 at p. 2100-1526, first column, second paragraph, the issue of written description "most typically...arise[s] in the context of determining whether new or amended claims are supported by the description of

the invention in the application as filed, whether a claimed invention is entitled to the benefit of an earlier priority date or effective filing date under 35 USC 119, 120 or 365(c) or whether a specification provides support for a claim corresponding to a count in an interference" [citations omitted]. The *Vas-Cath* case cited by the Examiner did arise in the typical context of determining new matter. Specifically, the issue was whether drawings of a catheter in a design application provided written description of claims that appeared in a utility application claiming priority to the design application. *Vas-Cath* does not address what written description is required for originally filed claims.

This issue is addressed by MPEP 2163 at p. 2100-156, second column et seq. which states that despite a "strong presumption that an adequate written description of the claim invention is present when the application is filed," "the issue of written description may arise even for an original claim" if the "claimed invention as a whole require[s] an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art." The issue of written description for original claims has most often arisen in the context of nucleic acids. The *Amgen, Fiddes,* and *Fiers* cases cited by the Examiner are well known examples of such cases.

In *Amgen*, the claims at issue were directed to nucleic acids encoding human erythropoietin, a protein that had not hitherto been cloned. The court held that one could not conceive of such nucleic acids until they had actually been isolated and sequenced. The *Amgen* court, however, did not "imply that generic claims to genetic sequences cannot be valid where they are of a scope appropriate to the invention disclosed by the application" (18 USPQ2d 1016, 1027 (Fed. Cir. 1991)). Similarly, in *Fiers*, the court held that one could not conceive of nucleic acids encoding human fibroblast beta interferon, another hitherto uncloned human protein, until such nucleic acids had actually been isolated and sequenced. Likewise, in *Baird*, the applicant was not in possession of the naturally occurring gene for bovine pituitary FGF or any other gene for any mammalian FGF at the time of filing.

Here, many of the present the claims have not changed substantially from the original claims, and no issues of new matter have been raised against any claim. The present case does not therefore fall under the typical ambit of written description addressed by MPEP

2163 at p. 2100-156, col. 1, second paragraph or by the *Vas-Cath* case. Rather, the present case arises in the less usual situation when the PTO has the burden of overcoming the "strong presumption" that the originally filed claims have adequate written description. Although the *Amgen Fiers* and, *Fiddes* cases do identify an exceptional circumstance when this presumption may be overcome, the present facts are substantially different than those in the *Amgen, Fiers* and *Fiddes* cases; hence, the exception does not apply here.

The present claims differ from those at issue in the *Amgen*, *Fiers, Fiddes* cases in that the invention lies not in de novo isolation of a gene but in mutation of a well-characterized class of molecules, i.e., antibodies. In circumstances in which the invention lies in cloning a gene, it is perhaps not unreasonable that a newly isolated gene cannot be described without determining its sequence. However, the PTO's Guidelines for application of the written description requirement explicitly recognize that a class of antibodies can be defined in functional terms without providing sequence data. The functional definition of an antibody is sufficient because of "the routine art-recognized method of making antibodies to fully characterized antigens, the well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature." *See* Example 6 of the Synopsis of Application of Written Description Guidelines. In keeping with these guidelines, numerous patents have issued in which antibodies are characterized in part or in whole by functional properties, such as binding affinity. For example, the antibodies in *Wands* are characterized by the property of a binding affinity of at least $10^9\ M^{-1}$ for a target antigen.

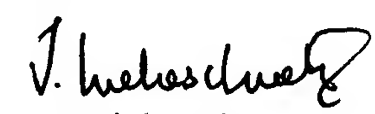
In view of the well-known structure of antibodies, and the description of glycosylation sites and how to remove them provided by the specification, and the Written Description Guidelines authorizing antibodies to be characterized at least in part by functional properties, and the unrelated facts and circumstances of the cited case law, it is respectfully submitted that the Examiner has not overcome the presumption of written description.

The method claims (46-48) satisfy written description for the same and additional reasons. Even if one does not know the exact structure of the product of a method, one can envisage each step of claims 46-48 needed to generate the product.

For all these reasons, withdrawal of the rejection is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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